BISPHOSPHOPHONATES

BACKGROUND

- Bisphosphonates are analogs of endogenous pyrophosphate in which a carbon atom replaces the central oxygen atom.
- Carbon substitution confers resistance to hydrolysis and allows two additional chains of varying structure.
- One of these side chains usually contains hydroxyl moiety, allowing high affinity for calcium crystals and bone mineral.
- Bisphosphonates have a high affinity for bone and are preferentially delivered to sites of increased bone formation or resorption.
- Once deposited on the surface of bone, are ingested by osteoclasts that are involved in bone resorption.
- Bisphosphonates are potent inhibitors of osteoclastic bone resorption and initially shown to be effective in treating cancer-induced hypercalcemia of malignancy, Paget's disease of bone, and postmenopausal osteoporosis.
- Subsequently, have been shown to be effective in patients with osteolytic bone metastases from breast cancer, skeletal complications from multiple myeloma, and bone metastases from other solid tumors including prostate and lung cancer.

TABLE 1. TYPES OF BISPHOSPHONATES

GENERIC NAME (BRAND NAME)	ROUTE	RELATIVE POTENCY*	INDICATION
Etidronate (Didronel®)	PO, IV	1	Osteoporosis (PO) Hypercalcemia (IV)
Clodronate (Bonefos®)	PO	10	Not approved in US
Tiludronate (Skelid®)	PO	10	Paget's disease Osteoporosis (?)
Pamidronate (Aredia®)	IV	100	Breast cancer Multiple myeloma Hypercalcemia
Alendronate (Fosamax®)	PO	1,000	Osteoporosis
Ibandronate (Boniva®)	PO	10,000	Osteoporosis
Risedronate (Actonel®)	PO	> 10,000 < 100,000	Osteoporosis Paget's disease
Zoledronic Acid (Zometa®)	IV	100,000	Myeloma Bone mets from solid tumors Hypercalcemia

*Relative to etidronate

BISPHOSPHONATES IN BREAST CANCER

ASCO Guideline on the Role of Bisphosphonates in Breast Cancer. Reference: *J Clin Oncol* 2000;18:1378 – 91.

- Expert panel under auspices of ASCO's Health Services Research Committee.
- Published literature through May 1999, ASCO annual meeting abstracts, FDA submissions.
- Evidence rated by group consensus.

ASCO 2003 Update. Reference: *J Clin Oncol* 2003;21:4042 – 57.

- Reviewed published data after 2000 (Medline, meeting abstracts, industry data), Cochrane Review.
- Includes bone health issues (due to increased use of aromatase inhibitors).

LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION

LEVEL	Type of Evidence
I	Evidence from meta-analysis of multiple, well designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II	Evidence from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).
III	Evidence from well designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, and time or matched case-control series.
IV	Evidence from case reports
GRADE	**Grade of Recommendation**
A	Evidence of level I or consistent findings from multiple studies of type II, III, or IV.
B	Evidence of level II, III, or IV and findings are generally consistent
C	Evidence of level II, III, or IV but findings are inconsistent
D	Little or no systematic empirical evidence

SUMMARY OF GUIDELINES:

1. Use in Women with Radiographic Evidence of Bony Metastases
   A. Lytic destruction on plain radiograph:
   2000 recommendation: IV pamidronate 90 mg IV over 1-2 hours Q3-4 weeks (along with hormonal therapy or chemotherapy) **(I, A).**
   2003 update: IV pamidronate 90 mg over 2 hrs or zoledronic acid 4 mg IV over 15 minutes Q3-4 weeks. Is insufficient evidence supporting one agent over the other?

   Note: There is a recent report (Reference: Rosen LS, et al. *Cancer* 2004;100:36 – 43) indicating that zoledronic acid may be superior to pamidronate in breast cancer patients with at least one osteolytic lesion. This is a retrospective subgroup analysis of data collected as part of a larger Phase III trial of zoledronic acid in patients with metastatic breast cancer and multiple myeloma. That initial publication demonstrated non-inferiority of zoledronic acid compared with pamidronate; with a similar proportion SREs (skeletal-related events) occurring during the 13-month study period in the treatment groups (43% with zoledronic acid 4 mg vs. 45% with pamidronate 90 mg).

   In the retrospective subgroup analysis in patients with at least one osteolytic lesion, zoledronic acid yielded an additional 17% relative reduction in SREs compared with pamidronate (48% vs. 58%, p=0.058). Of note, the SRE rate for pamidronate of 58% is higher than that reported in the original pamidronate studies (43% and 47% respectively, for patients receiving chemotherapy or hormonal therapy). Among patients in the non-lytic subgroup (those with mixed, primarily osetoblastic, or unknown lesions), there was no difference between zoledronic acid and pamidronate.

Within the lytic subgroup, zoledronic acid was statistically superior to pamidronate in several secondary efficacy analyses. Zoledronic acid prolonged the time to first SRE vs. pamidronate (median 310 days vs. 174 days, p = 0.013), and reduced the annual incidence of skeletal events (mean 1.2 per year vs. 2.4 per year, p = 0.008) compared with pamidronate. Again, there was no difference between zoledronic acid and pamidronate in the non-lytic group.

B. Abnormal bone scan and abnormal CT or MRI showing bone destruction along with localized pain, but with negative plain radiograph:
2000 recommendation: starting bisphosphonates is reasonable **(N/A, panel consensus)**.
2003 update: starting bisphosphonates is reasonable (**panel consensus)**.

C. Asymptomatic, abnormal bone scan, negative plain radiographs, CT scans, or MRI:
2000 recommendation: starting bisphosphonates is NOT suggested. **(N/A, panel consensus)**.
2003 update: no change.

2. Biochemical Markers:
2000 recommendation: use of biochemical markers to monitor bisphosphonate use is NOT suggested for routine care **(III, C)**.
2003 update: no change.

3. Duration of Therapy:
2000 recommendation: bisphosphonates should be continued until evidence of substantial decline in patient's overall performance status (based on clinical judgment) **(N/A, panel consensus)**.
2003 update: no change.

4. Pain Control secondary to bony metastases:
2000 recommendation: Bisphosphonate use should not displace current standards of care for pain management, analgesic use, and local radiation therapy. IV pamidronate is recommended in combination with systemic/hormonal therapy in patients with pain due to osteolytic metastases. **(I, A)**.
2003 update: no change.

5. No Radiographic Evidence of Bony Mets
A. Extraskeletal metastases without evidence of bony involvement:
2000 recommendation: starting bisphosphonates is NOT recommended. **(II for PO and N/A for IV, B for PO and panel consensus for IV)**.
2003 update: no change.

B. Bisphosphonates as Adjuvant Therapy:
2000 recommendation: starting bisphosphonates outside of clinical trial is NOT recommended. **(II, C)**.
2003 update: no change.

6. Osteoporosis Prevention:
2000 recommendation: oral bisphosphonates are one of several options that may be used to preserve bone mineral density in premenopausal women with treatment-induced menopause **(II, B)**.
2003 update: most women with newly diagnosed breast cancer are at risk of osteoporosis due to either their age or their breast cancer treatment. Panel recommended an algorithm for patient management to maintain bone health.

7. Safety and Adverse Effects (new 2003 recommendation): in patients with pre-existing renal disease and a serum creatinine level < 3 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is needed. Infusion times < 2 hrs for pamidronate or < 15 minutes for zoledronic acid should be avoided. Serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid.

THERAPIES FOR OSTEOPOROSIS PREVENTION AND TREATMENT

THERAPY	DOSAGE	SIDE EFFECTS	ISSUES IN BREAST CANCER PATIENTS
FDA-APPROVED BISPHOSPHONATES			
Alendronate Prevention/ Treatment	5 mg PO QD 35 mg PO QW 10 mg PO QD 70 mg PO QW	Upper GI irritation, myalgias, arthralgias	None
Ibandronate Prevention/ Treatment	150 mg PO Qmonth		
Risedronate Prevention/ Treatment	5 mg PO QD 35 mg PO QW		None
SERM			
Raloxifene Prevention/ Treatment	60 mg PO QD	Hot flashes, leg cramps. Rare: DVT	Cross-resistance with tamoxifen. Not recommended after Tamoxifen.
PARATHYROID HORMONE (SYNTHETIC)			
Teriparitide	20 units SC QD	Dizziness, leg cramps. Rare: hypercalcemia	Not recommended. Should not be used in patients at increased risk of bone metastases or hypercalcemia (due to osetosarcoma development in animal models).
Estrogen + Progestin Combination Prevention only	Varies	Breast tenderness, vaginal bleeding Life threatening: CHD, stroke, PE, breast cancer	Not recommended in patients with breast cancer when used for prevention of osteoporosis.
Estrogens Prevention only	Varies	Breast tenderness, vaginal bleeding Life threatening: CHD, stroke, PE, breast cancer	Not recommended in patients with breast cancer when used for prevention of osteoporosis.
Calcium	1200 mg/ day	Constipation, bloating, gas	None
Vitamin D	400 – 600 mg*	None	None
Calcitonin nasal spray	200 units one nostril/day	Rhinitis	None

*1 unit of Vitamin D equals 0.025 mcg cholecalciferol (vitamin D3). Recommended daily intake of Vitamin D is 400 – 800 units. Most multivitamins contain 400 units. Commercial forms of vitamin D3 are supplied in either 400 or 1000 unit tablets.

RECOMMENDED MANAGEMENT STRATEGY FOR PATIENTS WITH NEWLY DIAGNOSED BREAST CANCER

<table>
<tr><td colspan="4">Screen Patients for Osteoporosis Risk</td></tr>
<tr><td>Low Risk</td><td colspan="3">High Risk*</td></tr>
<tr><td rowspan="2">Screening for BMD
not recommended</td><td colspan="3">Screening for BMD recommended
DEXA of Hip +/- Spine</td></tr>
<tr><td>T Score ≤ -2.5</td><td>T Score between -1 and -2.5</td><td>T score > -1</td></tr>
<tr><td>Lifestyle Advice
Begin Calcium and Vitamin D</td><td>Lifestyle Advice
Begin Calcium and Vitamin D
Alendronate or Risedronate or Zoledronic Acid or Raloxifene</td><td>Lifestyle Advice
Begin Calcium and Vitamin D</td><td>Reassure
Lifestyle Advice
Begin Calcium and Vitamin D</td></tr>
<tr><td>Monitor Annually for Risk Status by History</td><td>Repeat BMD annually</td><td>Repeat BMD annually</td><td>Repeat BMD annually</td></tr>
</table>

*High Risk:

1) All women older than 65 yrs;
2) All women aged 60 - 64 years of age with family history, body wt less than 70 kg, prior non-traumatic fracture, or other risk factors;
3) Postmenopausal women of any age receiving aromatase inhibitors; *OR*
4) Premenopausal women with therapy-associated premature menopause.

BISPHOSPHONATES IN MULTIPLE MYELOMA

ASCO Clinical Practice Guidelines: The Role of Bisphosphonates in Multiple Myeloma. Reference: *J Clin Oncol* 2002;20:3719 – 36.

- Expert panel under auspices of ASCO's Health Services Research Committee.
- Published literature through January 2002, ASCO annual meeting abstracts.
- Evidence rated by group consensus.

LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATION

LEVEL	ividence
I	Evidence from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power).
II	Evidence from at least one well-designed experimental study. Randomized trials with high false-positive and/or negative errors (low power).
III	Evidence from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, and time or matched case-control series.
IV	Evidence from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies.
V	Evidence from case reports and clinical examples.
GRADE	**Grade of Recommendation**
A	Evidence of level I or consistent findings from multiple studies of type II, III, or IV.
B	Evidence of level II, III, or IV and findings are generally consistent.
C	Evidence of level II, III, or IV but findings are inconsistent.
D	Little or no systematic empirical evidence.

Summary of Guidelines:

1. Lytic Disease on Plain Radiograph: IV pamidronate 90 mg over at least 2 hrs or zoledronic acid 4 mg over 15 minutes Q3-4 weeks is recommended. **(II, B)**.
2. Monitoring: in patients with pre-existing renal disease and a serum creatinine less than 3 mg/dL, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Infusion times less than 2 hrs for pamidronate or less than 15 minutes for zoledronic acid should be avoided. **(V, D)**.
   - Panel recommends intermittent evaluation (every 3 – 6 months) for the presence of albuminuria and azotemia. In patient experiencing unexplained albuminuria (greater than 500 mg/24hrs) or azotemia (increase of $\geq$ 0.5 mg/dL in serum creatinine or absolute value $>$ 1.4 mg/dL in patients with normal baseline value), discontinuation of bisphosphonate is warranted until renal problems resolve. These patients should be reassessed Q3-4 weeks until renal function returns to baseline, the pamidronate resumed with a longer infusion time ($\geq$ 2 hrs) and at dose snot to exceed 90 mg Q4 weeks.
3. Duration of Therapy: Bisphosphonate should be continued until there is evidence of substantial decline in patient's performance status (based on clinical judgment). There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events. **(N/A, panel consensus)**.
4. Myeloma patients with Osteopenia based on normal plain radiographs or BMD measurements: It is reasonable to start bisphosphonates. **(N/A, panel consensus)**.
5. Patients with solitary plasmacytoma or smoldering or indolent myeloma without documented lytic bone disease: starting bisphosphonates is NOT recommended. **(N/A, panel consensus)**.
6. Patients with MGUS: starting bisphosphonates is NOT suggested. **(N/A, panel consensus)**.
7. Biochemical markers: use of biochemical markers of bone metabolism to monitor bisphosphonate use is not suggested for routine care. **(III, C)**.
8. Role in Pain Control Secondary to Bony Involvement: IV pamidronate or zoledronic acid is recommended for patient with pain due to osteolytic disease and as an adjunctive treatment for patients receiving radiation therapy, analgesics, or surgical intervention to stabilize fractures to impending fractures. **(II, B)**.

BISPHOSPHONATES IN OTHER SOLID TUMORS

Zoledronic Acid has been shown to have efficacy in patients with bone metastases due to lung cancer and other solid tumors, as well as metastatic prostate cancer.

Study	Pt Type	Drug/Dose	Evaluable pts	SRE (% pts)	SMR (events/yr)	Median Time to 1st SRE
Rosen et al JCO 2003	Solid Tumors (~50% NSCLC)	ZOL 4 mg ZOL 8/4 mg Placebo	257 266 250	38% 35% 44%	2.24 1.55** 2.52	230 days* 163 days
Saad et al. JNCI 2002	HRMPC	ZOL 4 mg ZOL 8/4 mg Placebo	214 221 208	33%* 39% 44%	0.8** 1.06 1.49	> 420 days* 363 days 321 days
Saad et al JNCI 2004	24 month f/up of above	ZOL 4 mg ZOL 8/4 mg Placebo	214 221 208	38%* 49%	0.77** 1.47	488 days** 321 days

*$p \leq 0.05$ vs. placebo; **$p \leq 0.01$ vs. placebo; NSCLC: non-small cell lung cancer; SRE: skeletal-related event; SMR: skeletal morbidity rate (excluding hypercalcemia); HRMPC: hormone-refractory metastatic prostate cancer.

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Brown JE, et al. The role of bisphosphonates in breast and prostate cancers. *Endocr Relat Cancer* 2004;11:207 - 24.

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Perry CM and Figgitt. Zoledronic Acid: A review of its use in patients with advanced cancer. *Drugs* 2004;64:1197 - 211.

Rosen LS, et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase II, double-blind, randomized trial - The Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150 - 7.

Saad F, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458 - 68.

Saad F, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst* 2004;96:879 - 82.

BISPHOSPHONATES AND OSTEONECROSIS OF THE JAWS

- Osteonecrosis of the jaws is a condition in which there is loss or destruction of the bone beneath the teeth. This bone loss is thought to be due to a combination of poor blood supply and impaired bone remodeling or healing.
- Reports began to appear in 2003 raising the possibility that osteonecrosis (or avascular necrosis) could be an unexpected complication of bisphosphonate therapy.
- The first published report came from a maxillofacial surgeon in Florida, who noticed that he was seeing more patients with osteonecrosis, and reported his findings on 36 patients, all of whom were taking either pamidronate or zoledronic acid. Eighteen of the 36 (50%) had multiple myeloma, and 17 (47%) had metastatic breast cancer. (Reference: Marx RE. *J Oral Maxillofac Surg* 2003;61:1115-8).
- Ruggiero et al reported their experience with 63 patients with osteonecrosis (44% had multiple myeloma, 32% had breast cancer) occurring during chronic bisphosphonate therapy. Eighty-eight percent of patients were taking either pamidronate or zoledronic acid. (Reference: Ruggiero SL, et al. *J Oral Maxillofac Surg* 2004;62:527-34).
- At ASCO 2004, Estilo et al from MSKCC reviewed all patients with breast cancer or myeloma who had been seen by their dental service. They identified 124 patients, 13 of whom developed osteonecrosis (9 with breast cancer, 4 with myeloma). (Reference: *Proc Am Soc Clin Oncol* 2004: abstract 8088).
- Language addressing the development of osteonecrosis was added to the FDA-approved labeling (package inserts) for both pamidronate and zoledronic acid.

Recommendations:

1. Be alert and aware that bisphosphonate use may be associated with jaw/dental problems, including pain, bone loss, and poor healing. Problems appear more likely to develop with longer periods of bisphosphonate use and (possibly) more potent bisphosphonates (i.e. zoledronic acid).
2. Be proactive if dental problems exist or if any dental or jaw interventions are planned. If feasible, dental evaluation prior to starting bisphosphonate may be a good idea.
3. Once bisphosphonate therapy has started, major dental procedures (extractions, implants, etc.) should be undertaken with caution. Stopping bisphosphonate therapy for 2 – 4 months prior to a planned procedure can be considered (although there is no definitive data to support this suggestion).
4. Good oral hygiene is essential.
5. Avoid tooth extractions or elective jaw surgery if at all possible. Root canal therapy and crowns are safe and may allow preservation of the tooth.

If osteonecrosis occurs:

1. Consultation with an oral surgeon or dental oncologist familiar with osteonecrosis is strongly recommended.
2. Management without surgery is recommended as first step. Minor dental work to reduce sharp edges or remove injured tissue maybe needed. A protective mouth guard may be helpful.
3. Antibiotic treatments are recommended for infection, with specific antibiotics selected based on the type of infection. Oral rinses (with chlorhexidine gluconate) or minocycline hydrochloride periodontal pockets may be also be used.
4. If problems persist or if healing is slow, stopping bisphosphonate therapy for 2-4 months can be considered.
5. If surgery is necessary, interruption of bisphosphonate therapy is strongly recommended.
6. Dentures may be worn, but may need adjustment. Dental implants should be avoided.
7. Careful monitoring and follow up are necessary.

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FDA Medwatch Dear Doctor Letter on Osteonecrosis of the Jaw. Available at: http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#zometa2.

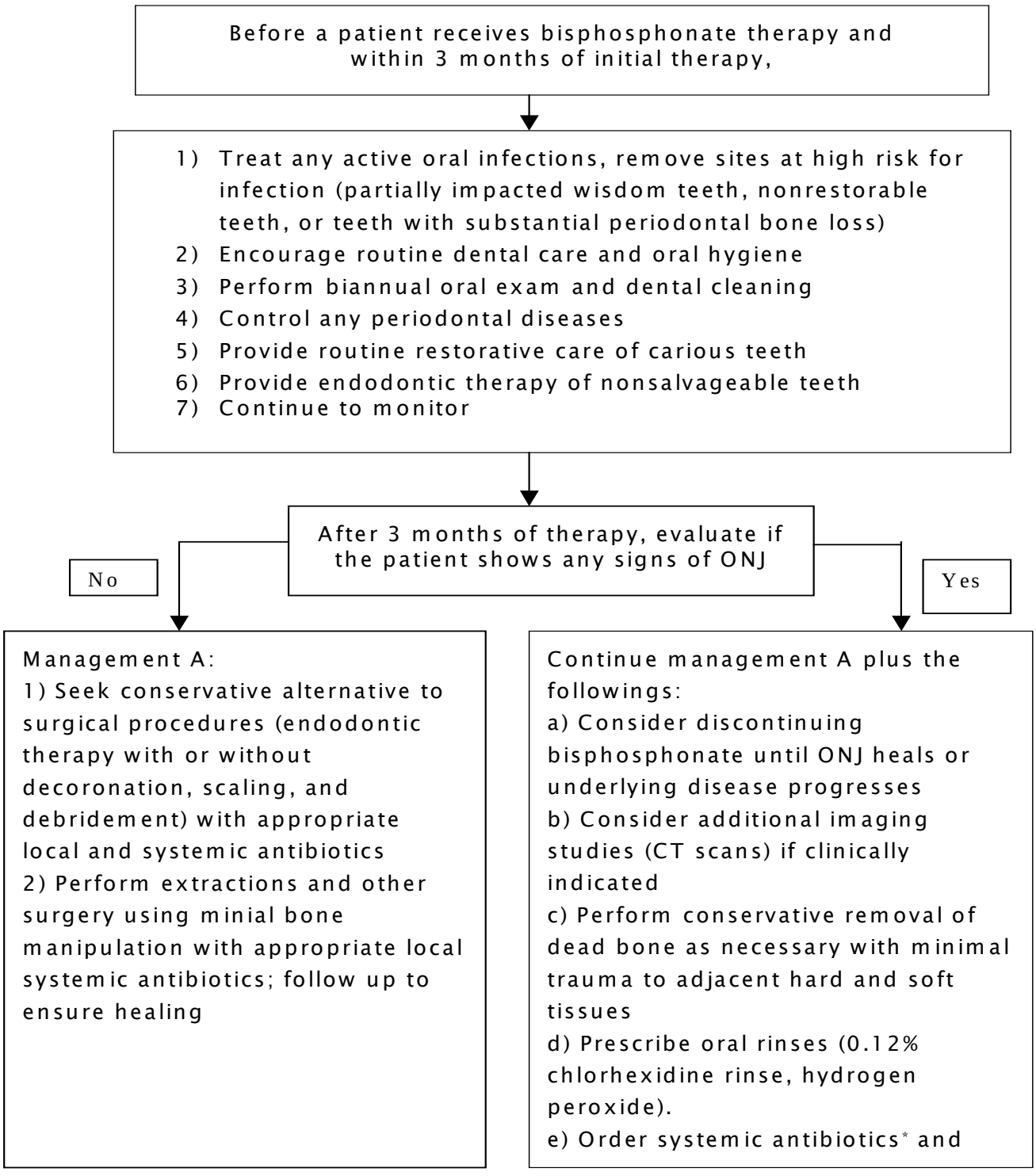
Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61:1115 – 8.

Mehrotra B, et al. Osteonecrosis of the maxilla: an unusual complication of prolonged bisphosphonate therapy. A case report. *Proc Am Soc Clin Oncol* 2003: abstract 3194.

Ruggiero SL, et al. Osteonecrosis of the jaws associated with bisphosphaontes: a review of 63 cases. *J Oral Maxillofac Surg*. 2004;62:527 – 34.

Prepared: Laura Wiggins, PharmD, BCOP., October 2004

RECOMMENDATIONS OF MANAGEMENT OF OSTEONECROSIS OF JAW ASSOCIATED WITH BISPHOSPHONATES



Examples of systemic antibiotics include monotherapy or combination therapy with beta-lactam, tetracycline, macrolide, metronidazole, and/or clindamycin.

Reference: Woo SB, et al. *Ann Intern Med* 2006;144:753-761; Erratum in *Ann Intern Med*. 2006;145:235.

Last Updated on January 15, 2007